UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,918	04/23/2007	Gabriele Multhoff	KNAUTHE-12014	1880

72960 7590 10/15/2010

Casimir Jones, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
10/15/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,918	MULTHOFF, GABRIELE	
	Examiner	Art Unit	
	HONG SANG	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8,15 and 56-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,15 and 56-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/5/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Multhoff

1. Applicant's response filed on 9/8/2010 is acknowledged. Claims 1-4, 6-8, 15 and 56-58 are pending. New claim 58 has been added. Claims 5, 9-14 and 16-55 have been cancelled. Claims 1, 56 and 57 have been amended.

2. Claims 1-4, 6-8, 15 and 56-58 are under examination.

Information Disclosure Statement

3. The information disclosure statement (IDS) filed on 10/5/2010 has been considered. A signed copy is attached hereto.

Priority

4. Applicant's submission of a new oath which claims priority benefits of foreign applications is acknowledged.

Specification

5. The objection to the disclosure because the Brief Description of the Drawings does not reference each of the Figures is withdrawn in view of applicant's amendment to the specification.

It is noted that applicant's amendment to the specification does not meet the requirement set forth in 37 CFR 1.121(b) (ii). Applicant failed to provide:

(ii) The full text of any replacement paragraph with markings to show all the changes relative to the previous version of the paragraph. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter

must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strikethrough cannot be easily perceived. See MPEP 714[R-6].

For compact prosecution, the amendment has been entered.

Objections Withdrawn

6. The objection of claim 57 because the amino acid residues 158-457 of BAG-4 are not really a C-terminal domain of BAG is withdrawn in view of applicant's amendment to the claim.

7. The objection to claims 56 and 57 because the claims recite specific amino acid residues without reciting the sequence of Hsp70 and Bag-4 is withdrawn in view of applicant's amendment to the claims.

Rejections Withdrawn

8. The rejection of claims 1-4, 6-7, 15, 56 and 57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicant's amendment to the claims.

9. The rejection of claim 5 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a bispecific immunoglobulin of claim 1, wherein the first binding domain is a first immunoglobulin antigen binding site (comprising all 6 CDRs, i.e. HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3), and the second binding domain is a second immunoglobulin antigen binding site (comprising all 6

CDRs, i.e. HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3) , does not reasonably provide enablement for a bispecific immunoglobulin of claim 1, wherein the first binding domain is a first immunoglobulin antigen variable region, and the second binding domain is a second immunoglobulin variable region is withdrawn in view of applicant's amendment to the claims.

Rejections Maintained

Claim Rejections - 35 USC § 103

10. The rejection of claims 1-4, 6-8, 15, 56 and 57 under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (US2005/0009033A1, Pub. Date: 1/13/2005, effective filing date: 7/8/2003), in view of Ozawa et al. (Biochem. Biophy. Res. Commun., 2000, 271: 409-413), Goeddel et al. (US 6,110,690, Date of Patent: 8/29/2000), Multhoff (WO 02/22656A2, Pub. Date: 3/21/2002), and Kortt et al. (Biomolecular Engineering, 2001, 18:95-108) is maintained.

The response states that claims have been amended to recite "the bispecific antibody specifically binds its antigen on variable cells". The response states that antibodies recognizing the carboxyl terminal amino acid residues 454-461 of Hsp70 specifically bind Hsp70 on tumor cells because those amino acid residues constitute a particular extracellular localized epitope of Hsp70, which is not visible or formed by Hsp70 intracellular or in its isolated form. Furthermore, Bag-4 (SODD) exerts its effect intracellularly, also other members of the Bag protein family such as Bag-1 are reported to bind to Hsc70 intracellularly. Accordingly, the prior art consistently teaches that the

Bag protein is localized in and exerts its effect including binding to Hsp70 or Hsc70 intracellularly. It indeed makes no sense to construct a bispecific molecule comprising one binding domain which specifically binds cells surface membrane bound Hsp protein and a second binding domain which antigen, i.e. Bag protein is localized intracellularly.

Applicant's arguments have been carefully considered but are not persuasive. Gray et al. disclose a method of inhibiting proliferation of a breast cancer cell in which BAG4 is amplified and overexpressed, the method comprising contacting the breast cancer cell with a therapeutically effective amount of a BAG4 antibody (see paragraphs [0009], [0010] and [0134]). As such Gray explicitly teaches that BAG4 is overexpressed on breast cancer cells, and an anti-BAG4 antibody can bind BAG4 expressed on breast cancer cells and treat breast cancer. Gray further teaches that the anti-BAG4 antibody may be a bispecific antibody having biding specificities for at least two different antigens, one of the binding specificities is for BAG4, the other one is for a tumor specific cell-surface protein or receptor (see paragraph [0133]). Thus Gray suggested making a bispecific antibody that binds to BAG4 and a tumor specific cell surface protein or receptor. Multhoff teaches that Hsp70 was specifically expressed on tumor cell membrane (see Example 1). The instant specification acknowledges that it was well known in the art at the time the invention was made that membrane bound Hsp70 was found specifically in tumor cells and susceptible to radiation treatment (see the specification page 3, paragraph 3). Ozawa et al. disclose that Hsp70 is commonly overexpressed in human tumors, and its expression in certain cancer types correlated with poor prognosis (see page 412, column 2, paragraph 2). Ozawa et al. disclose that

SODD (BAG-4) might also act by activating Hsp70/Hsc70 to TNFR-1 and thereby blocking the recruitment of death domain-containing adapter proteins (see page 412, column 2, paragraph 2). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a bispecific antibody that binds to BAG4 and Hsp70 in view of Gray, Multhoff and Ozawa. One would have been motivated to do so because Ozawa et al teach that SODD (BAG-4) might act by activating Hsp70/Hsc70 to TNFR-1 and thereby blocking the recruitment of death domain-containing adapter proteins (see page 412, column 2, paragraph 2). Given the teachings of the prior art that BAG4 may directly modulate the function of Hsp70, it would have been obvious to one skilled in the art to make a bispecific antibody that binds to Hsp70 and BAG4 in order to detect, and/or modulate the function of Hsp70 and/or BAG4. Applicant's arguments that Bag protein is only localized intracellularly are not persuasive. Eichholtz-Wirth (Anticancer Res. 2002, 22, 235-240, IDS submitted on 10/5/2010) discloses SODD/BAG4 may be membrane-associated and the amount of the membrane associated SODD/BAG4 can be altered by radiation treatment (see abstract and page 239). Furthermore, even if one skilled in the art would was motivated to make a bispecific antibody that binds BAG4 and intracellular Hsp70, such antibodies would still bind to membrane Hsp70 since neither the prior art nor the instant specification discloses that the membrane bound Hsp70 is structurally (for example amino acid sequence) different from the intracellular Hsp70 or isolated Hsp70. The binding domain recited in the claims broadly encompasses any binding domains that are capable of binding membrane Hsp (see claims 1, 3, 4, 6-8, 15 and 57), or capable

of binding to the C-terminal region of human Hsp70 (see claims 2 and 56). Claims as written do not preclude the binding domain from binding to intracellular Hsp and/or isolated Hsp. Applicant is reminded that while a bispecific antibody has the function of binding to two antigens simultaneously, it is not the sole reason for one skilled in the art to make a bispecific antibody. Lynch (US 2002/0155109A1, Pub. Date: 10/24/2002) teaches that a bispecific antibody offers advantages over a monospecific antibody in that: (a) if a particular type of cancer cells expresses either of the two receptors, the bispecific antibody would bind to these cells (see paragraph [0018]); (b) when an antibody binds a first receptor, the likelihood of a second receptor being physically proximate for binding by a second antigen binding site of the antibody generally will be greater when a bispecific antibody is employed, compared to a monospecific antibody (see [0019]); (c) if downregulation of the expression of one receptor occurs on target cancer cells during a course of treatment with a monospecific antibody, the cancer cells could become resistant to treatment with the monospecific antibody, use of a bispecific antibody may decrease the likelihood of such resistance development, since both receptors have to be dowregulated for the cells to become resistant (see paragraph [0020]). In the instant case, the prior art suggested that both BAG4 and Hsp70 are overexpressed in cancer, are both found in cell membrane, and BAG4 may directly modulate the function of Hsp70. Thus making a bispecific antibody that binds BAG4 and Hsp70, was clearly in the purview of those of ordinary skill in the art and was within the knowledge of those in the art at the time the invention was made.

New Grounds of Objections and Rejections

Claim Objections

11. Claim 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112, 1st paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 58 is rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

While the specification discloses that the hydridomas identified by Accession numbers DSM ACC2629 and DSM ACC2630 have been deposited (see the specification, page 12, lines 20-32), such a statement is not sufficient to satisfy the requirement for deposit of biological materials. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell

line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 112, 1st paragraph

14. Claim 58 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **new matter** rejection.

The phrase "derived from monoclonal antibody cmHsp70.1…or from cmHsp70.2" is considered new matter because it is not supported by the original disclosure.

The specification only discloses antibody cmHsp70.1 and cmHsp70.2. While one skilled in the art would consider applicant is in possession of a bispecific antibody comprising a binding domain comprising the VH and VL domains of the antibody cmHsp70.1 or cmHsp70.2, one would not consider applicant is in possession of a bispecific antibody comprising a binding domain that is derived from the antibody cmHsp70.1 or cmHsp70.2. "A binding domain derived from the antibody cmHsp70.1 or cmHsp70.2" includes variants resulted from modification of the amino acid sequence of cmHsp70.1 and cmHsp70.2 at any positions, including the amino acid residue(s) in their variable binding regions. The instant specification does not disclose such variants. As such the phrase "derived from monoclonal antibody cmHsp70.1…or from cmHsp70.2" broadens the scope of the binding domain as originally disclosed and introduces new matter.

If applicant believes that support for the above-mentioned phrases or terms is present in the specification, claims or drawing as originally filed, applicant must, in responding to this action, point out with particularity, where such support may be found.

Applicant is required to cancel the new matter in the reply to this Office Action.

Conclusion

15. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HONG SANG whose telephone number is (571)272-8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Hong Sang/
Examiner, Art Unit 1643

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1645